genetic associations may be masked by ethnic heterogeneity and, with age, by the increasing impact of hormonal and environmental factors.

1 Tikkanen MJ. Immunogenetic polymorphism of apolipoprotein B in man. Studies with a monoclonal anti-Ag(c) antibody. *Am Heart J* 1987;**113**:462-7.
2 Viikari J, Åkerblom HK, Nikkari T, *et al.* Atherosclerosis precursors in Finnish children and adolescents. IV. Serum lipids in newborns, children and adolescents. *Acta Paediatr Scand* 1985;**318** (suppl):103-9.
3 Berg K. DNA polymorphism at the apolipoprotein B locus is associated with lipoprotein level. *Clin Genet* 1986;**30**:515-20.
4 Talmud PJ, Barni N, Kessling AM, *et al.* Apolipoprotein B gene variants are involved in the determination of serum cholesterol levels: a study in normo- and hyperlipidaemic individuals. *Atherosclerosis* 1987;**67**:81-9.
5 Young SG, Bertics SJ, Scott TM, *et al.* Apolipoprotein B allotypes $MB19_1$ and $MB19_2$ in subjects with coronary artery disease and hypercholesterolemia. *Arteriosclerosis* 1987;**7**:61-5.

(Accepted 14 October 1987)

Third Department of Medicine, Meilahti Hospital, University of Helsinki, 00290 Helsinki
M J TIKKANEN, MD, acting associate professor

Department of Medicine, University of Turku
J VIIKARI, MD, associate professor

Children's Hospital, University of Helsinki
H K ÅKERBLOM, MD, professor, II department of paediatrics
E PESONEN, MD, paediatric cardiologist, I department of paediatrics

Correspondence to: Dr Tikkanen.

Transporting critically ill patients by ambulance: audit by sickness scoring

Patients who are critically ill may be safely transported by specialist teams[1] but no prospective studies to investigate the efficacy of transporting such patients by ordinary ambulances attended by junior doctors have been reported. Such studies are important because most critically ill patients are probably transported in this way. Financial constraints may result in increasing use of ordinary ambulances to transfer such patients to centralised units. We performed an audit of non-specialist transport within a district general hospital group in which a sickness score was used to control for severity of illness.

Patients, methods, and results

Vascular and general surgery, coronary care, and most medical specialties are sited within a five mile radius of this intensive care unit; patients are therefore commonly transferred to the unit by ambulances, the journey taking a maximum of 30 minutes. The unit accepts all patients except those with uncomplicated head injuries.

We studied 50 consecutive patients transferred to the unit. Severity of illness was assessed with a sickness score,[1] which is a modification of the acute physiology and chronic health evaluation (APACHE II) score.[2] The sickness score was calculated from data collected immediately before and after transport. Arterial blood samples for blood gas analysis were taken before transport, packed in ice, and analysed together with a sample drawn on arrival. Patients were not monitored during the journey. Controlled ventilation was provided with an Ambu bag; patients who had not been intubated received a controlled supply of oxygen from MC facemasks. The partial pressure of inspired oxygen was measured with an oxygen meter. Complications occurring during transfer and the seniority and specialty of the medical attendant were noted. Survival was taken as discharge home.

Of the 50 patients, 31 had had operations and 19 had medical conditions (repair of an aortic aneurysm 13; acute renal failure, 12; sepsis, seven; cardiac arrest, five; and respiratory problems, 13). Seven patients, three of whom had had operations, developed eight serious complications during transfer: obstruction of an endotracheal tube, respiratory arrest on arrival at the hospital, accidental disconnection of arterial and central venous cannulas, withdrawal of crucial inotropic and bronchodilator infusions (two cases), and unrecordable blood pressure on arrival (three). Six of the seven patients were attended by junior staff (registrar grade or below) who were not anaesthetists ($\chi^2=10{\cdot}79$, $p<0{\cdot}005$).

The table shows the numbers of patients and their mean sickness scores before and after transfer. The difference in scores between the survivors and non-survivors was highly significant ($p<0{\cdot}0001$). The mean score for non-survivors showed a small increase after transport, though this was not significant. Patients who suffered complications and those accompanied by junior staff or staff other than anaesthetists tended to have higher scores, but the differences were not significant.

Sickness scores (and 95% confidence intervals) before and after transport categorised by outcome, grade and specialty of attending staff, and complications

	No of patients	Mean sickness score	
		Before transport	After transport
Survivors	34	10·2 (8·9 to 12·0)	10·4 (9·1 to 12·2)
Non-survivors	16	19·0 (16·3 to 21·6)	20·6 (17·7 to 23·4)
Senior staff	27	12·0 (9·7 to 14·3)	12·5 (10·3 to 14·7)
Junior staff	23	14·1 (11·3 to 16·9)	15·0 (11·8 to 18·2)
Anaesthetists	34	12·4 (10·5 to 14·4)	13·0 (11·0 to 15·0)
Other	16	14·1 (10·4 to 17·9)	15·1 (10·8 to 19·3)
Complications	7	15·2 (10·1 to 20·4)	16·5 (10·2 to 22·9)
No complications	43	12·6 (10·7 to 14·5)	13·2 (11·2 to 15·2)

Comment

This study showed that life threatening complications may occur in critically ill patients when conventional ambulances are used for transport. Complications were more common in patients attended by junior doctors and doctors other than anaesthetists and were not due to more severe illness among these patients. The training in resuscitation received by anaesthetists may be an advantage in caring for patients when monitoring is not available. The complications were not the direct cause of death in any patient, probably because of the short journey; longer transport times might have resulted in a significant increase in sickness scores.

Because severity of illness was controlled for, these results suggest that inexperience in the management of patients who are critically ill is the dominant factor in the development of complications during transfer, confirming earlier work.[3] The results support the need for improved training in resuscitation[4] and suggest that blood pressure should be monitored during transfer.

1 Bion JF, Edlin SA, Ramsay G, McCabe S, Ledingham IMcA. Validation of a prognostic score in critically ill patients undergoing transport. *Br Med J* 1985;**291**:432-4.
2 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;**13**:818-29.
3 Waddell G, Scott PDR, Lees NW, Ledingham IMcA. Effects of ambulance transport in critically ill patients. *Br Med J* 1975;i:386-9.
4 Baskett PJF. Resuscitation needed for the curriculum? *Br Med J* 1985;**290**:1531-2.

(Accepted 30 September 1987)

Intensive Care Unit, Plymouth General Hospital, Plymouth PL4 8QQ
J F BION, MRCP, FFARCS, senior registrar
I H WILSON, FFARCS, registrar
P A TAYLOR, FFARCS, consultant

Correspondence to: Dr J F Bion, Department of Anaesthetics, Birmingham University, Birmingham B15 2TH.

Is altered cardiac sensation responsible for chest pain in patients with normal coronary arteries? Clinical observation during cardiac catheterisation

Most patients with chest pain characterised as angina pectoris have obstructive atheromatous disease of the coronary arteries. In a few patients with angina pectoris exercise testing indicates abnormalities but coronary angiograms are normal.[1] Various theories have been proposed to explain these findings, termed syndrome X, and which include abnormalities of coronary reserve or myocardial metabolism and abnormal histological appearances.[2-4] During routine cardiac catheterisation we observed that patients with syndrome X were unusually sensitive to intracardiac instrumentation. We report the findings of a preliminary study.

Patients, methods, and results

We studied seven patients with syndrome X (exertional chest pain associated with ST segment depression of more than 1 mm during exercise and normal coronary arteries); four patients with typical angina but negative results on exercise testing and normal coronary arteries; seven patients with atherosclerotic coronary artery disease; and nine patients with mitral valve disease.

Using a standard brachial or femoral approach we inserted disposable catheters into the right (venous) and left (arterial) sides of the heart after the patients had been given lorazepam as premedication. Patients with chest pain also underwent maximum incremental atrial pacing with continuous monitoring by 12 lead electrocardiography.

During catheterisation all patients with coronary artery and mitral valve disease were insensitive to movement of the catheter. In contrast, six of the seven patients with syndrome X and all four patients with chest pain and normal coronary arteries, although unaware of arterial catheterisation, experienced spontaneous but shortlived chest pain similar to that of which they had previously complained when the venous catheter was moved within the proximal 3-5 cm of the superior vena cava and the entire right atrium. This pain was consistently and rapidly provoked by turning and forward and backward movements of the catheter. As the venous catheters were moved within the vascular sheaths the patients were not aware of movements of the catheter through the skin. The inferior vena cava, right ventricle, pulmonary artery, and coronary sinus were also not sensitive to movement of the catheter.

Injection of 10 ml saline into the right atrium briefly provoked anginal pain, but a second and third injection did not; incremental increases in the volume of saline injected did not provoke pain until 50 ml was injected, when six out of 11 patients felt pain. Throughout the procedure there were no changes in right atrial pressure or the electrocardiograms.

Comment

We observed that in patients with angiographically normal coronary arteries typical chest pain was reproduced consistently by direct right atrial stimulation and infusion of saline. The perception of pain is subjective, and this study lacked an unequivocal, objective end point. Electrocardiographic changes were not observed. The brief duration of right atrial stimulation and chest pain was possibly an insufficient stimulus to induce electrocardiographic changes, which, anyway, need not indicate myocardial ischaemia in patients with syndrome X.[3]

The mechanism of chest pain in coronary artery disease remains poorly understood. Both atria and ventricles have liberal sensory innervation, and myocardial ischaemia stimulates non-myelinated sympathetic nerves by way of the cardiac plexus to the sympathetic ganglia from C7 to T4. The nature of this stimulus is unknown. It may be acidosis or a raised intracellular potassium concentration, but sympathetic afferent fibres also possess some mechanosensitivity.[5]

The mechanism of chest pain in syndrome X is less clear. In some patients hyperventilation and oesophageal or psychological factors may be relevant. Syndrome X, however, is a particularly heterogenous disorder, and some patients have abnormalities of coronary vasodilator reserve or myocardial metabolism.[2-4] Our observation suggests a further mechanism whereby chest pain may arise from altered awareness of the changes in right atrial pressure and volume that occur during exercise.

1 Proudfit WL, Shirey EK, Somes FM. Selective cine coronary arterography: correlation with clinical findings in 1000 patients. *Circulation* 1966;**33**:901-10.
2 Opherk D, Mall G, Zebe H, *et al*. Reduction of coronary reserve: a mechanism for angina pectoris in patients with arterial hypertension and normal coronary arteries. *Circulation* 1984;**69**:1-7.
3 Poole-Wilson PA. Potassium and the heart. *Clin Endocrinol Metab* 1984;**249**:68.
4 Richardson PJ, Livesley B, Oram S. Angina pectoris with normal coronary arteries. Transvenous myocardial biopsy in diagnosis. *Lancet* 1974;ii:677-80.
5 Malliani A, Lombardi F. Consideration of the fundamental mechanisms eliciting cardiac pain. *Am Heart J* 1982;**103**:575-8.

(Accepted 1 October 1987)

National Heart Hospital and Cardiothoracic Institute, London
LEONARD M SHAPIRO, MD, MRCP, senior registrar
TOM CRAKE, MB, MRCP, registrar
PHILIP A POOLE-WILSON, MD, FRCP, professor of cardiology

Correspondence to: Dr L M Shapiro, National Heart Hospital, London W1M 8BA.

Hyperthyroidism after gonadotrophic ovarian stimulation

We report two cases of hyperthyroidism associated with pharmacological ovarian stimulation in patients with underlying autoimmune thyroiditis.

Case reports

Case 1—A 29 year old woman was admitted for in vitro fertilisation and embryo transfer because of her husband's infertility. Her history was unremarkable. Tests of thyroid function yielded normal results: free triiodothyronine concentration was 3·9 pmol/l (normal 2·8-5·6 pmol/l), free thyroxine concentration 9·2 pmol/l (normal 6·6-14·0 pmol/l), and thyroid stimulating hormone concentration 1·4 mU/l (normal 0·1-6·0 mU/l). Antibodies to thyroglobulin and microsomal antibodies were present (1/10 and 1/25 600, respectively), and the concentration of immunoglobulins inhibiting binding of thyroid stimulating hormone was 6·5 U/l (normal <10 U/l). All hormonal determinations were performed with commercially available radioimmunoassay kits. From day 3 after the onset of menses follicular stimulation was initiated with clomiphene citrate 100 mg twice daily for five days and enhanced by menotrophin (Humegon, Organon) follicle stimulating hormone 75 IU and luteinising hormone 75 IU/phial) twice daily from day 7. When the follicles were sufficiently mature ovulation was induced by one injection of two phials of human chorionic gonadotrophin (Pregnyl, Organon; 5000 U/phial). During this procedure the patient developed symptoms of hyperthyroidism: free triiodothyronine concentration was more than 28·7 pmol/l, free thyroxine concentration greater than 48·7 pmol/l, and thyroid stimulating hormone concentration less than 0·1 mU/l. The serum oestradiol concentration was 4767 pmol/l (ovulation occurs at oestradiol concentrations of 1830-11000 pmol/l). She was cured after 18 months of treatment with propylthiouracil 100 mg thrice daily.

Case 2—Graves' disease was diagnosed in 1983 in a 34 year old woman. She was successfully treated with methimazole. In 1986 she was admitted for in vitro fertilisation and embryo transfer, the indication being andrological. Tests of thyroid function yielded normal results: free triiodothyronine concentration was 6·6 pmol/l; free thyroxine concentration was 13·5 pmol/l; thyroid stimulating hormone concentration was 4·5 mU/l; microsomal antibodies were present (1/25 600); and the concentration of immunoglobulins inhibiting binding of thyroid stimulating hormone was 5 U/l. After a few days of treatment with menotrophin (Humegon) and before human chorionic gonadotrophin was given she developed symptoms of hyperthyroidism. Free triiodothyronine concentration was 9·7 pmol/l, free thyroxine concentration 29·9 pmol/l, and thyroid stimulating hormone concentration less than 0·1 mU/l. The serum oestradiol concentration was 4584 pmol/l. No antithyroid drugs were given apart from beta blockade; treatment with menotrophin was stopped. Three weeks later all signs of hyperthyroidism resolved and the results of thyroid function tests returned to normal.

Comment

Although hyperthyroidism may have developed by chance in these patients with underlying autoimmune thyroiditis, the close temporal relation between ovarian stimulation and the occurrence of hyperthyroidism, and the spontaneous resolution of symptoms in case 2 after follicular stimulation was stopped, suggest that other mechanisms may have been implicated.

As thyrotoxicosis that develops in the course of trophoblastic diseases has been postulated to be due to the stimulating effects of human chorionic gonadotrophin on the thyroid[1] and as temporary aggravation of Graves' disease during early pregnancy coincides with maximal serum concentrations of human chorionic gonadotrophin[2] might human chorionic gonadotrophin have been a possible causal factor in at least case 1? Hyperthyroidism in trophoblastic disease, however, seems to be mediated by thyroid stimulating, acidic isoelectric variants of human chorionic gonadotrophin, which are present only in low concentrations in the serum of pregnant women[3]; in vivo studies with crude human chorionic gonadotrophin failed to show appreciable stimulation of the thyroid in euthyroid men.[4] Furthermore, our second patient developed hyperthyroidism during treatment with menotrophin before human chorionic gonadotrophin had been given. Though luteinising hormone (present in menotrophin) shows a close structural analogy with human chorionic gonadotrophin, it has, to our knowledge, never been shown to stimulate the thyroid. Therefore the hypothesis that human chorionic gonadotrophin (luteinising hormone) alone was the causal agent seems weak.

Factors other than human chorionic gonadotrophin such as an appropriate hormonal environment[5] and pre-existing autoimmune thyroid disease may have a role. Thyroid antibodies were not measured in the cases of trophoblastic disease associated with hyperthyroidism reported by Nisula and Ketelslegers.[1] Pharmacological ovarian stimulation induces an important hormonal imbalance with high oestrogen concentrations. An eventual role for hyperoestrogenism in the pathogenesis of thyroid overactivity is difficult to assess as the interactions of oestrogen with the hypothalamopituitary-thyroid axis are complex and their exact nature poorly documented.

We postulate that the interplay of factors resulting from pharmacological ovarian stimulation and pre-existing autoimmune thyroid disease may have precipitated hyperthyroidism in our two patients.

This work was supported by grant 3.0059.85 from the Belgian Medical Research Council. We thank Mrs A Spiegeleer for preparing the manuscript.

1 Nisula BC, Ketelslegers JM. Thyroid-stimulating activity and chorionic gonadotrophin. *J Clin Invest* 1974;**54**:494-9.
2 Amino N, Tanizawa O, Mori H, *et al*. Aggravation of thyrotoxicosis in early pregnancy and after delivery in Graves' disease. *J Clin Endocrinol Metab* 1982;**55**:108-12.
3 Mann K, Schneider N, Hoermann R. Thyrotropic activity of acidic isoelectrical variants of human gonadotrophin from trophoblastic diseases. *Endocrinology* 1986;**118**:1558-66.